UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,068	08/18/2000	John R. Stuelpnagel	067234-0110	6751

41552 7590 02/21/2008
MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
02/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/642,068	STUELPNAGEL ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5,7,9,10,27-30,33-37 and 52-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,7,9,10,27-30,33-37 and 52-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007 has been entered.

2. Claims 2-10, 27-31 and 33-53 were previously pending. Applicants cancelled claims 2, 6, 8, 31 and 38-51, amended claims 3, 5, 7, 9, 27-30, 33-35, 52 and 53, and added new claims 54-60. Claims 3-5, 7, 9, 10, 27-30, 33-37 and 52-60 are pending and will be examined.

3. Applicants' amendments overcame the following: rejection of claims 2-10, 27-31 and 33-53 under 35 U.S.C. 112, first paragraph, written description; rejection of claims 2-10, 27-31 and 33-53 under 35 U.S.C. 112, second paragraph; rejection of claims 2, 6, 8, 31 and 38-51 under 35 U.S.C. 103(a) over Pastinen et al. and Lipshutz et al., as evidenced by Sinha et al.; rejection of claim 52 under 35 U.S.C. 103(a) over Beattie et al. and Lipshutz et al. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

4. This office action contains new grounds for rejection necessitated by amendment, as well as restament of previously presented rejections. Applicants' arguments are addressed regarding the restated rejections since they rely mostly on previously presented prior art references.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on December 19, 2007 was filed after the mailing date of the final office action on June 27, 2007. The submission is in compliance with

the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

6. Applicant's arguments filed October 30, 2007 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 2, 5-10, 27-31 and 33-51 under 35 U.S.C. 103(a) over Pastinen et al. and Lipshutz et al., as evidenced by Sinha et al., Applicants argue the following:

i) The rejection does not mention a finding that there would have been a reasonable expectation of success when combining the cited reference. In particular, Applicants argue that using a mixture of oligonucleotides obtained from the method of Lipshutz et al. as primers in PCR method of Pastinen et al. would not have been expected to produce desirable amplification results, since the complex mixture of primers provided by Lipshutz et al. would produce spurious amplification results.

ii) Lipshutz et al. does not provide a description of using the oligo pools as primers, and Pastinen et al. teach away from using the pools of Lipshutz et al. as primers. Applicants argue that the statement of Pastinen et al. can be understood as a statement that there are limits to the number of genomic fragments that can be produced using PCR methods, and that has nothing to do with primer availability.

iii) Applicants further discuss a reference of Syvanen et al., published in 2001, which addressed the issue of spurious result production in multiplex amplification were pools of oligonucleotides were used. Applicants reiterate that therefore one of ordinary skill in the art would have no expectation of success using oligo pools of Lipshutz et al. as primers. Applicants further argue that pools of primers could not be used in amplification since pools of more than 10 primer

pairs would result in spurious amplification products. Since Lipshutz et al. teach pools having at least 20 oligonucleotides with different sequences, the pool of this complexity would not work in the method of Pastinen et al.

B) Regarding the rejection of claims 3 and 4 under 35 U.S.C. 103(a) over Pastinen et al. and Lipshutz et al., as evidenced by Sinha et al., and further in view of Nelson et al., Applicants argue that since the combination of Pastinen et al. and Lipshutz et al. does not anticipate the independent claims, the rejection is improper.

C) Regarding the rejection of claims 52 and 53 under 35 U.S.C. 103(a) over Beattie et al. and Lipshutz et al., Applicants argue that the claims were amended to add a limitation of an array of randomly distributed probe oligonucleotides. Applicants further argue that the examiner has to prove that the subject matter in the rejection based on Beattie et al. is present in the provisional application that preceded the Beattie et al. patent, otherwise the rejection is improper.

Regarding A) i), ii) and iii), pools of oligonucleotides were used in amplification reactions since the invention of PCR, at least 10 years before Applicants' invention, since the PCR reaction mix usually contains at least two primers. In fact, none of the claims require more than two different oligonucleotides to be used in further processing after being released from the array, therefore, since amplification reactions with two primers have been used in the art for at least twenty years, one of ordinary skill in the art would have no problem expecting this approach to succeed, provided primers are correctly designed. The last issue is a key to Applicants' arguments that one would not expect a pool of more than 10 primer pairs to work in a multiplex amplification if they were produced by the method of Lipshutz et al. However, the problem here is not whether the pools are created by the method of Lipshutz et al. or by mixing together individually-synthesized primers, but whether the primers are designed in a way which would ensure that they

would work together in a highly multiplexed amplification reaction, the problem which has nothing to do with the way they are synthesized. Finally, successful multiplexing of amplification reactions was known in the art at least a year before Applicants' filing date.

First, Shuber et al. (Genome Res., vol. 5, pp. 488-493, 1995) designed primers for successful amplification of 15 CFTR gene loci in a single PCR reaction (page 490, paragraphs 2-5; page 491, paragraphs 2-4; Fig. 2 and 3). Therefore, Shuber et al. successfully amplified target nucleic acids using a pool of 30 different primers which contained a universal primer sequence at their 5' ends. Similar primer design, although not described in detail, allowed Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998) to successfully amplify sets of 23, 46 or 92 loci, requiring 46, 92 or 184 primers in a single reaction, respectively (page 1080, third paragraph). Further, Wang at al. amplified 558 loci simultaneously with 50% success rate, i.e., a pool of 558 primers worked properly in a single PCR multiplex reaction.

In conclusion, one of ordinary skill in the art familiar with the art would not expect that using multiple oligonucleotides, i.e., a pool of oligonucleotides, in the PCR reaction would lead to failure based on the evidence presented above, and based on the fact that primer design software was very common and widely used in the art at the time of the invention, allowing optimized design of primers to be used in multiplex amplification reactions.

The rejection is maintained in a restated format.

Regarding B), the combination of Pastinen et al. and Lipshutz et al. was addressed above.

The rejection is maintained.

Regarding C), Applicants did not amend claim 53 to include the limitation of an array with probes randomly distributed on the substrate, therefore the rejection of claim 53 is maintained. As to the priority date of the subject matter of the Beattie et al. patent, all of the matter relied on in the

presented rejection is present in the priority application 60/106,655, filed on November 2, 1998, as can be ascertained by Applicants by accessing Public Pair and comparing the provisional application with the Beattie et al. patent.

The rejection is maintained.

Double Patenting

7. Claim 55 is objected to under 37 CFR 1.75 as being a duplicate of claim 28. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim interpretation

8. The following interpretation of claim limitations is used to evaluate correspondence between the current claims and prior art:

A) Applicants defined the term "pool" in the following way (page 8, last paragraph): "By "pool" is meant a plurality or more than one solution-phase oligonucleotide."

B) The term "first and second linkers" is interpreted as linkers which may be the same, as there is no requirement that they have to be different.

C) The term "chip" in claim 29 is interpreted as any substrate (it is used interchangeably with "substrate" in the claim. Applicants' definition on page 16, fourth paragraph: "... By "chip" or biochip" herein is meant a planar substrate to which nucleic acids are directly or indirectly attached."

D) Applicants did not define the term "array" therefore any arrangement of oligonucleotides bound to a solid support is considered to be an array.

E) Applicants did not define the term "modifying oligonucleotides", therefore any reaction involving the oligonucleotides is considered to be their modification.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejections based on the Pastinen et al. reference

11. Claims 5, 7, 9, 10, 27-30, 33-37, 53, 55 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Res., vol. 7, pp. 606-614, 1997; cited in the previous office action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action), Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), Shuber et al. (Genome Res., vol. 5, pp. 488-493, 1995) and Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998).

Since claim 29 is specie of claims 27 and 30 and claims 33 and 35 are restated versions of claim 27, claim 55 is identical to claim 28, and claims 28, 34 and 53 differ from claim 29 by the support being beads, only steps of claim 29 are discussed explicitly, i.e., claims 27-30, 33-35, 53 and 55 are considered together in claim 29.

A) Regarding claims 27-30, 33-35, 53 and 55, Pastinen et al. teach a method of multiplex detection of target nucleic acids, the method comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first oligonucleotide and, wherein said second subpopulation comprises at least a second oligonucleotide, wherein said first oligonucleotide is different from said second oligonucleotide and, wherein said first and second oligonucleotides are of known sequence, said first and second oligonucleotides being immobilized directly to said substrate through first and second cleavable linkers, respectively (Pastinen et al. teach synthesis of amplification primers on Applied Biosystems 392 DNA synthesizer (page 610, third paragraph; page 612, Table 2), therefore they inherently teach synthesis of at least two different oligonucleotides immobilized to a substrate through cleavable linkers.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides (Pastinen et al. teach synthesis of amplification primers on Applied Biosystems 392 DNA synthesizer (page 610, third paragraph; page 612), therefore they inherently teach cleaving the oligonucleotides from the support, since the oligonucleotides are in the purified form and unattached to the substrate.);

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides (Pastinen et al. teach multiplex amplification of six genes in a single reaction, therefore they inherently teach hybridization of at least 12 primers to their respective six target sequences (page 611, second paragraph).);

d) modifying said first and second oligonucleotides hybridized with said first and second target nucleic acids to produce modified first and second oligonucleotides (Pastinen et al. teach multiplex amplification of six genes in a single reaction, therefore they inherently teach modification of at least 12 primers to their respective six target sequences (page 611, second paragraph).);

e) contacting said modified first and second oligonucleotides with an array comprising a substrate and a population of probe oligonucleotides comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first probe oligonucleotide and, wherein said second subpopulation comprises at least a second probe oligonucleotide, wherein said first and second probe oligonucleotides have sequences different from each other, wherein said first and second oligonucleotides are of known sequence, and, wherein said probe oligonucleotides have sequences different from said first and second oligonucleotides released from said substrate, whereby said target nucleic acids are detected Pastinen et al. teach contacting the amplified (=modified) sequences with an array of capture probes which have sequences different from each other and from the primers to detect the amplified sequences (page 610, last paragraph; page 611; page 612; page 613, first paragraph; Fig. 2).).

Regarding claims 57 and 58, Pastinen et al. teach PCR (page 611, second paragraph).

B) Pastinen et al. do not teach obtaining the primers from a pool of oligonucleotides released from a support it was synthesized on.

C) Lipshutz et al. teach a method of obtaining oligonucleotide pools.

Regarding claims 27-30, 33-35, 53 and 55, Lipshutz et al. teach multiplex detection of target nucleic acids, the method comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first oligonucleotide and, wherein said second subpopulation comprises at least a second oligonucleotide, wherein said first oligonucleotide is different from said second oligonucleotide and, wherein said first and second oligonucleotides are of known sequence, said first and second oligonucleotides being immobilized directly to said substrate through first and second cleavable linkers, respectively (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

Regarding claims 28, 34, 53 and 55, Lipshutz et al. do not specifically teach the substrate being beads. However, they teach synthesis of oligonucleotides on controlled pore glass (CPG) (col.

21, line 7) and synthesis by the method of Sinha et al. (col. 20, lines 24, 25). Sinha et al. teaches synthesis of oligonucleotides on CPG beads (page 4544, last paragraph). Therefore, by teaching synthesis of oligonucleotides by the method of Sinha et al. Lipshutz et al. inherently teach synthesis on glass beads.

Regarding claim 5, Lipshutz et al. teach covalent attachment of oligonucleotides to the substrate (col. 17, lines 57-67; col. 18, lines 1-9; col. 21, lines 4-33).

Regarding claim 7, Lipshutz et al. teach a substrate with a discrete sites (col. col. 16, lines 47-66).

Regarding claim 9, Lipshutz et al. teach synthesizing the oligonucleotides on a substrate (col. 16, lines 47-67; col. 17-19).

Regarding claim 10, Lipshutz et al. teach printing and photolithography (col. 17, lines 18-67; col. 18-19).

Regarding claim 36, Lipshutz et al. teach glass (col. 17, lines 57, 58).

Regarding claim 37, Lipshutz et al. teach a chip (col. 17, lines 13-16 and 57-60).

Regarding claims 59 and 60, Lipshutz et al. teach at least 20 and at least 50 different oligonucleotides (col. 2, lines 16-23; col. 6, lines 32-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as primers in the mutation detection method of Pastinen et al. with a reasonable expectation of success. One of ordinary skill in the art faced with the teachings of Pastinen et al. and Lipshutz et al. would have a choice of how the primers used in the multiplex amplification reaction were obtained, i.e., by the method of oligonucleotide pool synthesis of Lipshutz et al.or by an equivalent method using automatic DNA synthesizers such as the one used by Pastinen et al. However, in view of teaching of Weiler et al.

(Anal. Biochem., vol. 243, pp. 218-227, 1996), one of ordinary skill in the art might be motivated to choose the method of Lipshutz et al. Specifically, Weiler et al. teach synthesis of oligonucleotides on polypropylene sheets (= solid support) in such a way that the oligonucleotides could either remain bound to the support or could be cleaved and used as primers in an amplification reaction (Abstract; page 219; page 220, paragraphs 1-4; Fig. 6; Fig. 7; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Weiler et al. found that the quality of oligonucleotides synthesized on the array was sufficient to produce the same results as commercially available primers, even though they were not further purified after being released from the substrate (Fig. 7 and 8; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Therefore, one clear advantage of using primers synthesized on an array would be that they needed no further purification steps after being released from the substrate, unlike primers synthesized of commercially available DNA synthesizers, such as the one used by Pastinen et al. Weiler et al. points to other advantages of using oligonucleotides immobilized on arrays (page 226, last paragraph):

"The complete and efficient separation of nucleobase deprotection and release from the solid support, the stability of the succinate linker during hybridization, and the high quality of the oligomer molecules suggest a combined use of the arrays both as an instrument for screening experiments and as source for oligonucleotide primers. Thereby, an oligomer could first serve as a detector molecule, immediately followed by its use for an isolation of the appropriate DNA fragment by PCR or a direct tag sequence analysis of the region. Also, oligonucleotides identified by hybridization of a given DNA could in turn be used as probes for the identification of homologous fragments, for example, an approach that would simplify and speed up comparative genome analyses. For some applications, it might be necessary to introduce a stretch of unspecific

bases at the 3' terminus in order to ensure an enzymatic extension of the molecules by a polymerase. Due to combinatorial constraints, only a moderate number of sequence variations can be synthesized in parallel on a device of a type as depicted in Fig. 1. Nevertheless, such kind of array is of interest for diagnostic applications, for example. Moreover, the results suggest that ultimately even a larger number of independent oligonucleotides could be generated by an appropriately adjusted device. This could make techniques that require small amounts of different oligonucleotides such as primer walking sequencing even more functional."

Therefore, one of ordinary skill in the art at the time of the invention, faced with the choice of which method of synthesis of oligonucleotides to use for production of primers in multiplex amplifications would be motivated to use the method of pool synthesis of Lipshutz et al. in view of clear evidence from Weiler et al. that the primers could be used directly after cleavage from support, therefore saving time and expense required purification of oligonucleotides obtained from standard synthesis. Further, having the oligonucleotides immobilized on a support provided a clear advantage of being able to use them simultaneously in different assays, such as solution phase PCR and hybridization detection.

Finally, there would be a reasonable expectation of success as evidenced by at least two references cited below. First, Shuber et al. (Genome Res., vol. 5, pp. 488-493, 1995) designed primers for successful amplification of 15 CFTR gene loci in a single PCR reaction (page 490, paragraphs 2-5; page 491, paragraphs 2-4; Fig. 2 and 3). Therefore, Shuber et al. successfully amplified target nucleic acids using a pool of 30 different primers which contained a universal primer sequence at their 5' ends. Similar primer design, although not described in detail, allowed Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998) to successfully amplify sets of 23, 46 or 92 loci, requiring 46, 92 or 184 primers in a single reaction, respectively (page 1080, third

paragraph). Further, Wang at al. amplified 558 loci simultaneously with 50% success rate, i.e., a pool of 558 primers worked properly in a single PCR multiplex reaction.

12. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Res., vol. 7, pp. 606-614, 1997; cited in the previous office action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action), Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), Shuber et al. (Genome Res., vol. 5, pp. 488-493, 1995) and Wang et al. (Science, vol. 280, pp. 1077-1082, May 1998), as applied to claims 27-30, 34, 35, 53 and 55 above, and further in view of Nelson et al. (Nucl. Acids Res., vol. 20, pp. 6253-6259 (1992).

A) Lipshutz et al. teach fluorescence detection of hybrids (col. 25, lines 43-46), but do not teach labeling of the synthesized oligonucleotides.

B) Regarding claims 3 and 4, Nelson et al. teach labeling oligonucleotides during the synthesis step using labeled phosphoramidites (Abstract; page 6255, last paragraph; page 6256, paragraphs 1-5; Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have labeled the oligonucleotides of Lipshutz et al. and Pastinen et al.using the method of Nelson et al. The motivation to do so, provided by Nelson et al., would have been that the oligonucleotides were used directly in PCR amplification and quantitation, mRNA isolation, FISH analysis, antisense gene regulation, DNA fragment analysis and triple helix formation (page 6258, last paragraph).

Rejections based on the Beattie et al. reference

13. Claims 3-5, 7, 9, 10, 27-30, 33-37, 53, 55, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (U.S. Patent No. 6,268,147 B1; cited in the previous office

action) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action) and Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996).

Since claim 29 is specie of claims 27 and 30 and claims 33 and 35 are restated versions of claim 27, claim 55 is identical to claim 28, and claims 28, 34 and 53 differ from claim 29 by the support being beads, only steps of claim 29 are discussed explicitly, i.e., claims 27-30, 33-35, 53 and 55 are considered together in claim 29.

A) Regarding claims 27-30, 33-35, 53 and 55, Beattie et al. teach a method of multiplex detection of target nucleic acids, the method comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first oligonucleotide and, wherein said second subpopulation comprises at least a second oligonucleotide, wherein said first oligonucleotide is different from said second oligonucleotide and, wherein said first and second oligonucleotides are of known sequence, said first and second oligonucleotides being immobilized directly to said substrate through first and second cleavable linkers, respectively (Beattie et al. teach synthesis of oligonucleotides by standard phosophoramidite method, and synthesis of four auxiliary probes with sequences different from each other (col. 19, lines 49-59; col. 20, lines 31-56), therefore they inherently teach synthesis of at least two different oligonucleotides immobilized to a substrate through cleavable linkers.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides (Beattie et al. teach synthesis of oligonucleotides by standard phosophoramidite method (col. 19, lines 49-59), therefore they inherently teach cleaving the

oligonucleotides from the support, since the oligonucleotides are in the purified form and unattached to the substrate (col. 20, lines 31-56).);

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides (Beattie et al. teach contacting auxiliary probes with their respective target sequences so that they hybridize to these sequences (Fig. 13; Fig. 14A; col. 20, lines 31-56).);

d) modifying said first and second oligonucleotides hybridized with said first and second target nucleic acids to produce modified first and second oligonucleotides (Beattie et al. teach ligation (= modification) of the auxiliary probes to the capture probes (col. 12, lines 47-67). Beattie et al. also teach contacting the auxiliary probes labeled to their respective targets with capture probes bound to a solid support, where the sequences of the capture probes are different from the sequences of auxiliary probes (Fig. 8A; Fig. 13; Fig. 14A; col. 7, lines 66, 67; col. 8, lines 1-64). In this embodiment, the modification step is the step of binding to the capture probe, therefore steps d) and e) are performed simultaneously.);

e) contacting said modified first and second oligonucleotides with an array comprising a substrate and a population of probe oligonucleotides comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first probe oligonucleotide and, wherein said second subpopulation comprises at least a second probe oligonucleotide, wherein said first and second probe oligonucleotides have sequences different from each other, wherein said first and second oligonucleotides are of known sequence, and, wherein said probe oligonucleotides have sequences different from said first and second oligonucleotides released from said substrate, whereby said target nucleic acids are detected (Beattie et al. teach contacting the hybridized

sequences with an array of capture probes which have sequences different from each other and from the auxiliary probes to detect the amplified sequences (Fig. 8A; Fig. 13; Fig. 14A; col. 7, lines 66, 67; col. 8, lines 1-64).).

Regarding claims 3 and 4, Beattie et al. teach oligonucleotides labeled with different labels (col. 8, lines 20-23).

B) Beattie et al. teach using pools of oligonucleotides and chemical synthesis of oligonucleotides, but do not teach producing pools of oligonucleotides by cleaving oligonucleotides from an array.

C) Lipshutz et al. teach creation of oligonucleotide pools.

Regarding claims 27-30, 33-35, 53 and 55, Lipshutz et al. teach creation of oligonucleotide pools by:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides, respectively, said first and second oligonucleotides being immobilized to first and second beads, respectively, through first and second cleavable linkers, respectively, said first and second beads being distributed on said substrate (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said first and second beads, thereby generating a pool of oligonucleotides comprising said first and second different oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said first and second oligonucleotides with a first and second target nucleic acid (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

Regarding claims 28, 34, 53 and 55, Lipshutz et al. do not specifically teach the substrate being beads. However, they teach synthesis of oligonucleotides on controlled pore glass (CPG) (col. 21, line 7) and synthesis by the method of Sinha et al. (col. 20, lines 24, 25). Sinha et al. teaches synthesis of oligonucleotides on CPG beads (page 4544, last paragraph). Therefore, by teaching synthesis of oligonucleotides by the method of Sinha et al. Lipshutz et al. inherently teach synthesis on glass beads.

Regarding claim 5, Lipshutz et al. teach covalent attachment of oligonucleotides to the substrate (col. 17, lines 57-67; col. 18, lines 1-9; col. 21, lines 4-33).

Regarding claim 7, Lipshutz et al. teach a substrate with a discrete sites (col. col. 16, lines 47-66).

Regarding claim 9, Lipshutz et al. teach synthesizing the oligonucleotides on a substrate (col. 16, lines 47-67; col. 17-19).

Regarding claim 10, Lipshutz et al. teach printing and photolithography (col. 17, lines 18-67; col. 18-19).

Regarding claim 36, Lipshutz et al. teach glass (col. 17, lines 57, 58).

Regarding claim 37, Lipshutz et al. teach a chip (col. 17, lines 13-16 and 57-60).

Regarding claims 59 and 60, Lipshutz et al. teach at least 20 and at least 50 different oligonucleotides (col. 2, lines 16-23; col. 6, lines 32-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as probes in the mutation

detection method of Beattie et al. with a reasonable expectation of success. One of ordinary skill in the art faced with the teachings of Beattie et al. and Lipshutz et al. would have a choice of how the probes used in the multiplex detection reaction were obtained, i.e., by the method of oligonucleotide pool synthesis of Lipshutz et al.or by an equivalent method using automatic DNA synthesizers such as the one used by Beattie et al. However, in view of teaching of Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), one of ordinary skill in the art might be motivated to choose the method of Lipshutz et al. Specifically, Weiler et al. teach synthesis of oligonucleotides on polypropylene sheets (= solid support) in such a way that the oligonucleotides could either remain bound to the support or could be cleaved and used as primers in an amplification reaction (Abstract; page 219; page 220, paragraphs 1-4; Fig. 6; Fig. 7; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Weiler et al. found that the quality of oligonucleotides synthesized on the array was sufficient to produce the same results as commercially available primers, even though they were not further purified after being released from the substrate (Fig. 7 and 8; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Therefore, one clear advantage of using oligonucleotides synthesized on an array would be that they needed no further purification steps after being released from the substrate, unlike oligonucleotides synthesized on commercially available DNA synthesizers, such as the one used by Beattie et al. Weiler et al. points to other advantages of using oligonucleotides immobilized on arrays (page 226, last paragraph):

"The complete and efficient separation of nucleobase deprotection and release from the solid support, the stability of the succinate linker during hybridization, and the high quality of the oligomer molecules suggest a combined use of the arrays both as an instrument for screening experiments and as source for oligonucleotide primers. Thereby, an oligomer could first serve as a detector molecule, immediately followed by its use for an isolation of the appropriate DNA

fragment by PCR or a direct tag sequence analysis of the region. Also, oligonucleotides identified by hybridization of a given DNA could in turn be used as probes for the identification of homologous fragments, for example, an approach that would simplify and speed up comparative genome analyses. For some applications, it might be necessary to introduce a stretch of unspecific bases at the 3' terminus in order to ensure an enzymatic extension of the molecules by a polymerase. Due to combinatorial constraints, only a moderate number of sequence variations can be synthesized in parallel on a device of a type as depicted in Fig. 1. Nevertheless, such kind of array is of interest for diagnostic applications, for example. Moreover, the results suggest that ultimately even a larger number of independent oligonucleotides could be generated by an appropriately adjusted device. This could make techniques that require small amounts of different oligonucleotides such as primer walking sequencing even more functional."

The motivation to do so, provided by Beattie et al., was stated by Beattie et al. (col. 5., lines 30-41):

"There is furthermore a need for improved techniques for analysis of nucleic acid samples of high genetic complexity, using sequence-targeted oligonucleotide array hybridization. Also, there is a need for improved profiling of gene expression using numerous oligonucleotide probes targeted to mRNA species. Moreover, there is a need for more efficient identification of species, strains and individuals using DNA probe arrays designed to hybridize with numerous unique nucleotide sequences. There is in addition a need to adapt oligonucleotide array hybridization to directly analyze nucleic acid samples without the use of additional steps of target sequence amplification, single strand isolation and labeling."

Therefore, the availability of oligonucleotide pools of Lipshutz et al. as probes in the detection method of Beattie et al. would allow efficient genotyping using microarrays by providing

pools of oligonucleotides which did not require a time-consuming step of purification and could be produced in large quantities.

14. Claims 52, 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (U.S. Patent No. 6,268,147 B1; cited in the previous office action), Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action) (as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action) and Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996)), Walt et al. (U.S. Patent No. 6,327,410 B1) and Michael et al. (Anal. Chem., vol. 70, pp. 1242-1248, April 1998).

Since claim 56 is specie of claims 52 and 54, only steps of claim 56 are discussed explicitly, i.e., claims 52, 54 and 56 are considered together in claim 56.

A) Regarding claims 52, 54 and 56, Beattie et al. teach a method of multiplex detection of target nucleic acids, the method comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first oligonucleotide and, wherein said second subpopulation comprises at least a second oligonucleotide, wherein said first oligonucleotide is different from said second oligonucleotide and, wherein said first and second oligonucleotides are of known sequence, said first and second oligonucleotides being immobilized directly to said substrate through first and second cleavable linkers, respectively (Beattie et al. teach synthesis of oligonucleotides by standard phosophoramidite method, and synthesis of four auxiliary probes with sequences different from each other (col. 19, lines 49-59; col. 20, lines 31-56), therefore they inherently teach synthesis of at least two different oligonucleotides immobilized to a substrate through cleavable linkers.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides (Beattie et al. teach synthesis of oligonucleotides by standard phosophoramidite method (col. 19, lines 49-59), therefore they inherently teach cleaving the oligonucleotides from the support, since the oligonucleotides are in the purified form and unattached to the substrate (col. 20, lines 31-56).);

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides (Beattie et al. teach contacting auxiliary probes with their respective target sequences so that they hybridize to these sequences (Fig. 14A; col. 20, lines 31-56).);

d) modifying said first and second oligonucleotides hybridized with said first and second target nucleic acids to produce modified first and second oligonucleotides (Beattie et al. teach ligation (= modification) of the auxiliary probes to the capture probes (col. 12, lines 47-67). Beattie et al. also teach contacting the auxiliary probes labeled to their respective targets with capture probes bound to a solid support, where the sequences of the capture probes are different from the sequences of auxiliary probes (Fig. 8A; Fig. 13; Fig. 14A; col. 7, lines 66, 67; col. 8, lines 1-64). In this embodiment, the modification step is the step of binding to the capture probe, therefore steps d) and e) are performed simultaneously.);

e) contacting said modified first and second oligonucleotides with an array comprising a substrate and a population of probe oligonucleotides comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first probe oligonucleotide and, wherein said second subpopulation comprises at least a second probe oligonucleotide, wherein

said first and second probe oligonucleotides have sequences different from each other, wherein said first and second oligonucleotides are of known sequence, and, wherein said probe oligonucleotides have sequences different from said first and second oligonucleotides released from said substrate, whereby said target nucleic acids are detected (Beattie et al. teach contacting the hybridized sequences with an array of capture probes which have sequences different from each other and from the auxiliary probes to detect the hybridized sequences (Fig. 8A; Fig. 13; Fig. 14A; col. 7, lines 66, 67; col. 8, lines 1-64).).

B) Beattie et al. teach using pools of oligonucleotides and chemical synthesis of oligonucleotides, but do not teach producing pools of oligonucleotides by cleaving oligonucleotides from an array.

C) Lipshutz et al. teach creation of oligonucleotide pools.

Regarding claims 52, 54 and 56, Lipshutz et al. teach creation of oligonucleotide pools by:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides, respectively, said first and second oligonucleotides being immobilized to first and second beads, respectively, through first and second cleavable linkers, respectively, said first and second beads being distributed on said substrate (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said first and second beads, thereby generating a pool of oligonucleotides comprising said first and second different oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said first and second oligonucleotides with a first and second target nucleic acid (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as probes in the mutation detection method of Beattie et al. with a reasonable expectation of success. One of ordinary skill in the art faced with the teachings of Beattie et al. and Lipshutz et al. would have a choice of how the probes used in the multiplex detection reaction were obtained, i.e., by the method of oligonucleotide pool synthesis of Lipshutz et al.or by an equivalent method using automatic DNA synthesizers such as the one used by Beattie et al. However, in view of teaching of Weiler et al. (Anal. Biochem., vol. 243, pp. 218-227, 1996), one of ordinary skill in the art might be motivated to choose the method of Lipshutz et al. Specifically, Weiler et al. teach synthesis of oligonucleotides on polypropylene sheets (= solid support) in such a way that the oligonucleotides could either remain bound to the support or could be cleaved and used as primers in an amplification reaction (Abstract; page 219; page 220, paragraphs 1-4; Fig. 6; Fig. 7; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Weiler et al. found that the quality of oligonucleotides synthesized on the array was sufficient to produce the same results as commercially available primers, even though they were not further purified after being released from the substrate (Fig. 7 and 8; page 224, second, fourth and fifth paragraphs; page 226, first paragraph). Therefore, one clear advantage of using oligonucleotides synthesized on an array would be that they needed no further purification steps after being released from the substrate, unlike oligonucleotides synthesized on commercially available DNA synthesizers, such as the one used by Beattie et al. Weiler et al. points to other advantages of using oligonucleotides immobilized on arrays (page 226, last paragraph):

"The complete and efficient separation of nucleobase deprotection and release from the solid support, the stability of the succinate linker during hybridization, and the high quality of the oligomer molecules suggest a combined use of the arrays both as an instrument for screening experiments and as source for oligonucleotide primers. Thereby, an oligomer could first serve as a detector molecule, immediately followed by its use for an isolation of the appropriate DNA fragment by PCR or a direct tag sequence analysis of the region. Also, oligonucleotides identified by hybridization of a given DNA could in turn be used as probes for the identification of homologous fragments, for example, an approach that would simplify and speed up comparative genome analyses. For some applications, it might be necessary to introduce a stretch of unspecific bases at the 3' terminus in order to ensure an enzymatic extension of the molecules by a polymerase. Due to combinatorial constraints, only a moderate number of sequence variations can be synthesized in parallel on a device of a type as depicted in Fig. 1. Nevertheless, such kind of array is of interest for diagnostic applications, for example. Moreover, the results suggest that ultimately even a larger number of independent oligonucleotides could be generated by an appropriately adjusted device. This could make techniques that require small amounts of different oligonucleotides such as primer walking sequencing even more functional."

The motivation to do so, provided by Beattie et al., was stated by Beattie et al. (col. 5., lines 30-41):

"There is furthermore a need for improved techniques for analysis of nucleic acid samples of high genetic complexity, using sequence-targeted oligonucleotide array hybridization. Also, there is a need for improved profiling of gene expression using numerous oligonucleotide probes targeted to mRNA species. Moreover, there is a need for more efficient identification of species, strains and individuals using DNA probe arrays designed to hybridize with numerous unique nucleotide

sequences. There is in addition a need to adapt oligonucleotide array hybridization to directly analyze nucleic acid samples without the use of additional steps of target sequence amplification, single strand isolation and labeling."

Therefore, the availability of oligonucleotide pools of Lipshutz et al. as probes in the detection method of Beattie et al. would allow efficient genotyping using microarrays by providing pools of oligonucleotides which did not require a time-consuming step of purification and could be produced in large quantities.

D) Beattie et al. and Lipshutz et al. teach detection of analytes on arrays, but do not teach arrays with oligonucleotides distributed randomly on the surface of the array.

E) Regarding claims 52, 54 and 56, Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads are randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 54-56). The bioactive agent attached to the microsphere is a nucleic acid, particularly a nucleic acid probe (col. 7, lines 55-66; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). Walt et al. teach the microspheres containing a probe (=identifier binding ligand) which binds a decoder binding ligand (= target nucleic acid) (col. 10, lines 43-47; col. 21, lines 17-60). Since each of the beads contains a unique optical signature (col. 13, lines 8-24), the identity and location of each bead can be determined.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the randomly distributed oligonucleotides bound to microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid detection of

Beattie et al. and Lipshutz et al. The motivation to do so, provided by Walt et al., would have been that (col. 3, lines 13-26):

"The innovation of the two previous patents was the placement of multiple chemical functionalities at the end of a single optical fiber bundle sensor. This configuration yielded an analytic chemistry sensor that could be remotely monitored via the typically small bundle. The drawback, however, was the difficulty in applying the various chemistries associated with the chemical functionalities at the sensor's end; the functionalities were built on the sensor's end in a serial fashion. This was a slow process, and in practice, only tens of functionalities could be applied. Accordingly, compositions and methods are desirable that allow the generation of large fiber optic arrays including microspheres that can be either encoded or decoded to allow the detection of target analytes." and (col. 4, lines 35-56):

"The present invention is based on two synergistic inventions: 1) the development of a bead-based analytic chemistry system in which beads, also termed microspheres, carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality of each bead using an optically interrogatable encoding scheme (an "optical signature"); and 2) the use of a substrate comprising a patterned surface containing individual sites that can bind or associate individual beads. This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be "decoded", i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the

array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art."

Further motivation to use such arrays is provided by Michael et al. (Anal. Chem., vol. 70, pp. 1242-1248, April 1998) on page 1247, last paragraph, continued on page 1248:

"We have demonstrated the ability to fabricate randomly ordered, addressable, high-density optical sensor arrays. This approach to preparing array sensors offers a dramatic shift from conventional sensor fabrication procedures which require multiple steps such as photolithography, micromachining, and site-selective syntheses. Microwell arrays are easily and reproducibly fabricated using commercially available imaging fibers without requiring a high degree of precision. One series of chemical reactions can create a stock supply of billions (5.8×10^9 microspheres/mL) of chemically modified sensors with virtually identical properties that can be used in the fabrication of new arrays for different analyte sets. Also, the need to identify every location and to calibrate each sensor in the array is eliminated because only those microspheres giving rise to an analytical signal need to be decoded. This advantage may be of particular value when rapid diagnostic tools are required or when analyses with low "hits" are performed, such as immunodiagnostics or low-frequency mutation analysis with gene arrays. Multiple copies of each sensor are easily represented in each array, providing a level of redundancy that should avoid both false positives and false negatives. The image processing software used to analyze the spectral information makes this approach advantageous in applications requiring high sample throughput. Since the fabrication process is fast and simple and the materials are inexpensive, there is no economical demand to reuse the array. We are presently extending this work to demonstrate arrays for immunoassays, gene probe sequences, and vapor sensors. Finally, the sensors offer the ultimate flexibility-as new assays

come along, new microspheres simply can be added to the existing microsphere mixture at virtually no setup or time cost."

15. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
2/15/08